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EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/689,225	CANTOR ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *5-9 and 11-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/05/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.0.0

DETAILED ACTION

This Application, filed October 20, 2003, claims priority to U.S. Provisional Application, filed October 29, 2002.

Claims 1-15 are pending.

Election/Restrictions

Applicant's election without traverse of urine as the biological fluid and reversal of the light-dark cycle as the pre-selected perturbance in the reply filed on April 15, 2005 is acknowledged.

Claims 5-9, 11-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on April 15, 2005.

Claims 1-4, 10, drawn to a method for predicting adverse responses to drugs effecting a target by assessing the responses of animal models, is under consideration.

Information Disclosure Statement

The information disclosure statement filed August 5, 2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein

has not been considered. Reference AP, Campbell et al. (1996), is listed on the IDS, but no copy has been provided. If Campbell et al. is to be considered, a copy of the publication must be provided.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of predicting adverse responses to drugs effecting a target by assessing the responses of non-human mammalian models in

a transgenic mouse comprising a disruption of an endogenous gene of interest in its genome, wherein the transgenic mouse exhibits a phenotype correlated with the gene disruption and

a transgenic mouse comprising a transgene construct, comprising a nucleic acid sequence encoding a gene of interest operably linked to a promoter, wherein the construct is stably integrated in its genome, and wherein the transgenic mouse exhibits a phenotype correlated with overexpression of the gene of interest,

does not reasonably provide enablement for a method of predicting adverse responses to drugs effecting a target by assessing the responses of non-human mammalian models in

a genetically engineered mouse comprising a transplant transfected with any expression construct comprising a nucleic acid sequence encoding a gene of interest operably linked to a promoter, wherein the mouse exhibits a phenotype correlated with overexpression of the gene of interest,

a genetically engineered mouse comprising an episomal expression construct comprising a nucleic acid sequence encoding a gene of interest operably linked to a promoter, wherein the mouse exhibits a phenotype correlated with overexpression of the gene of interest,

any genetically engineered non-human mammal wherein said mammal exhibits either overexpression or underexpression of a target gene, other than transgenic mice .

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claimed invention is drawn to a method for predicting adverse responses to drugs effecting a target by assessing the responses of non-human mammalian models, is under consideration.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the

necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claimed invention broadly encompasses the use of any genetically engineered non-human mammal. Genetically engineered non-human mammal encompasses non-human mammals that are transgenic wherein the transgene is stably integrated into the host's genome, non-human mammals comprising a eukaryotic expression vector that is episomal (i.e. gene therapy), and non-human mammals comprising a transplant comprising a transgene construct.

With regards to non-human transgenic mammals comprising a transgene stably integrated into the host genome, the art teaches that making non-human

mammals by nuclear injection of a transgene is unpredictable. One reason for this unpredictability stems from the randomness in which the transgene integrates into the host's genome. Cameron (1997, Molecular Biotechnology, 7: 253-265) teaches, "a feature common to many transgenic experiments is the unpredictability transgenic lines produced with the same construct frequently displaying different levels of expression. Further, expression levels do not correlate with the number of transgene copies integrated. Such copy-number-independent expression patterns emphasize the influence of surrounding chromatin on the transgene (Cameron, page 256, section 4 on transgene regulation and expression)." Thus, an artisan cannot predict where a transgene will integrate in the host genome, how many copies of a transgene will integrate into the host genome, what the transgene expression pattern is, of the resulting transgenic animal (with regards to how much transcript is produced by the cell and with regards to in which tissues express transgene, as enhancers from the host's genome may also influence transgene expression), and what the subsequent phenotype(s) is of the transgenic animal. As summarized by Mench (1999, Transgenic Animals in Agriculture, eds. Murray et al., CAB International: Oxon, pages 251-268), "because there can be so much variation in the sites of gene insertion, the numbers of gene copies transferred, and gene expression, every transgenic animal produced using microinjection is (theoretically, at least) unique in terms of its phenotype (Mench, page 259, bottom)." An art example demonstrating the unpredictability in making transgenic animals is illustrated by Hammer et al. (1990, Cell, 6: 1099-1112). Hammer et al. created both

transgenic mice and rats expressing the human HLA-b27 gene and beta-2 microglobulin. Although both transgenic animals bearing the HLA-b27 gene expressed the gene, transgenic mice did not show any HLA-b27 associated disease, whereas the transgenic rats demonstrated most of the HLA-b27 related diseases (Hammer, et al., page 1099, col. 2, lines 20-28). This shows that the integration of a transgene into an alternative species may result in widely different phenotype responses even in animals of the same species. Additionally, promoters and enhancer elements may not function in all the species because they may require specific cellular factors. Further, Hammer et al. teach that while the transgenic mice and rats expressed human HLA-b27, only rats exhibited a phenotype similar to the human disease. This suggests that HLA-b27 does not behave similarly in mice as it does in humans and rats.

Hammer et al.'s example also illustrates that the promoter is unpredictable. While the transgenic mice and rats expressed the transgene, it is unclear whether the problem of the mice not exhibiting the phenotype depended on the fact that the mice could not drive the heterologous promoter to produce enough transgene product. The unpredictability in using a heterologous promoter is illustrated by Cowan et al. (2003, Xenotransplantation, 10: 223-231). Cowan et al. teach that promoters of three human genes, ICAM-2, hCRPs, and PECAM-1, which are predominantly expressed in vascular endothelium in mice and pigs. When tissue specific expression was measured, it was found that while mice showed a distinct expression profile of the three human genes, the tissue expression profiles of the three human gene promoters were distinctly

different in pigs. The authors concluded that "promoter performance in mice and pigs was not equivalent," and that "the weak expression driven by the human ICAM-2 promoter in pigs relative to mice suggests the need for additional regulatory elements to achieve species-specific gene expression in pigs. While the art teaches the unpredictability in using a heterologous promoter, the specification at the time of filing does not teach how to overcome the unpredictability in the art, in using any heterologous promoter. For an artisan to characterize every heterologous promoter in every species of non-human mammals, in order to overcome the unpredictability in use of any heterologous promoter is undue experimentation.

With regards to the instant invention, the specification does not teach how to make any transgenic non-human animals comprising a transgene construct. By "make" the Examiner means teaching an artisan what characteristics comprise the transgenic non-human mammal, such that any artisan could use the transgenic non-human mammal. These characteristics include disclosing what heterologous protein was used, what heterologous promoter was used, and what were the phenotype(s) exhibited by the transgenic non-human mammal. As such, because the art teaches that there is unpredictability in expressing heterologous protein and the specification does not teach an artisan how to overcome this unpredictability, for an artisan to make all different species of non-human mammals expressing all the different heterologous proteins from all species of non-human mammals is undue experimentation. Therefore, the

specification does not enable an artisan to practice the claimed invention for any transgenic animal.

The claimed invention broadly encompasses the use of non-human mammals comprising transgene constructs, wherein the transgene construct is injected into a non-human animal (i.e. gene therapy). With regards to injecting a non-human mammal with a non-viral DNA construct that could be expressed in eukaryotic cells, the specification does not teach a skilled artisan how to make a non-viral DNA construct that could be expressed in eukaryotic cells. These issues include selection of a heterologous promoter and selection of a heterologous gene of interest that is to be expressed in the animal. In addition to addressing how to make the transgene construct, the specification would need to address how the transgene construct would be administer. However, the specification does not teach how to administer such construct. The art teaches several ways that non-viral DNA eukaryotic vectors could be introduced into cells. For example, Wolff et al. teach that some methods of directly introducing non-viral DNA vectors into the animal include non-viral DNA encapsulated in liposomes, Non-viral DNA entrapped in proteoliposomes containing viral envelope receptor proteins, calcium phosphate-coprecipitated DNA, and DNA coupled to polylysine-glycoprotein carrier complex (Wolff, et al., 1990, Science, 247: 1465-1468; page 1465, 1st col., 1st parag., lines 11-18). Wolff et al. teach that non-viral DNA vectors can also be directly injected into muscle. However, the non-viral DNA vector, depending on its route of administration, only localizes

to certain tissues or organs. As a result, the vector is not readily distributed throughout the body. For example, Wolff et al. show that the non-viral DNA is localized to the muscle at the site of injection (Wolff, et al., page 1465, 3rd col., 2nd parag.) Nicolau et al. demonstrated that non-viral DNA suspended in liposomes are localized to the liver and the spleen (Nicolau, et al., 1983, PNAS, USA, 80: 1068-1072; page 1068, 1st col., 1st parag.). Another problem associated with using non-viral DNA vectors is that they suffer from inefficient gene transfer. Abdallah et al. (1995, Biol. Cell., 85: 1-7) teach that one of the major hurdles in using non-viral DNA *in vivo* is successfully having the vector enter the nucleus (Abdallah, et al., page 2, 1st col., 2nd parag.). In addition to this, expression from these non-viral vectors is transient (Somia and Verma, 2000, Nature Reviews, 1:91-99; page 91, 1st col., 2nd parag., lines 2-8)). While it may be that the instant invention is to expressing a transgene in the liver or muscle, and the time of expression required to use the instant invention transient, the specification does not teach that these are the embodiments which are used to practice the claimed invention. For that matter, the specification does not teach that a skilled artisan that the instant invention has these certain limitations and can be used in certain applications. The claims encompass embodiments such as duration of transgene expression. However, the art teaches that use of any transgene would need to be empirically determined, based on what the transgene is and what effect an artisan is expecting, based on the expression of the transgene. An artisan would need to determine if long-term or short-term of gene expression is required for his/her study, determine whether or not the

means of introducing a non-viral DNA expression vector is sufficient for duration of the study and whether the transgene is expressed at detectable levels. To determine these parameters require undue experimentation. In addition to these parameters, a skilled artisan needs to also consider the fact that gene transfer from non-viral vectors is unpredictable. In other words, it may not even be a salient system to use for gene expression. For reasons of unpredictability and undue experimentation, the specification has not enabled a skilled artisan to reliably obtain mice injected with a non-viral transgene construct.

With regards using a viral vector as a vehicle to deliver a nucleic acid encoding a gene of interest, the art teaches that viral vectors as a vehicle is unpredictable. These issues of unpredictability include immune responses to the transgene product, the dose of virus administered, the promoter chosen to drive expression of the recombinant gene, the innate immune mechanisms and direct cytotoxcity cause by expression of viral genes (e.g. see Somia and Verma, page 92, Box 1). In addition to this, while an adenoviral vector remains episomal, and expresses a transgene transiently, some viral vectors, such as retroviral, lentiviral, and adeno-associated viral, will integrate into the genome and express for life-long expression of the transgene (Somia and Verma, page 91, 2nd col., 2nd parag.). However, one major problem with viral vectors that integrate in the host's genome is that the integration is random. In addition to the problem of random integration being that transcription of the transgene may then become under the control of neighboring factors of the host genome, the problem with random integration is that the transgene may integrate and disrupt a vital gene

(Somia and Verma, page 93, 2nd col., 1st parag., see also, page 92, Box 1). For these reasons, the use of a viral vector is determined empirically. However, the specification as filed does not provide sufficient guidance, working examples, and evidence as to how an artisan of skill would have made and used the claimed invention commensurate with the scope of the claims without undue experimentation.

With regards to the situation wherein a transplant comprising a transgene is administered to a non-human mammal, the art teaches that the art of transplantation is unpredictable. With regards to a xenogeneic or allogeneic transplant, one major problem associated with these transplants is loss or rejection of the cell. The loss or rejection stems from an immune response to the foreign cell (Platt, 1998, Nature, 392 supplement: 11-17; page 11, 2nd col. under "The barriers to xenotransplantation". While one might use drugs to immunosuppress a host, the specification does not teach what those drugs may be nor does the specification teach how to administer such drugs (which drugs, how much, route of delivery, for what duration of time). In addition to this, a skilled artisan would need to know how to prevent infection of the host organism, while the host's immune system is suppressed (Platt, page 14, Box 1, 1st parag.). One may suggest that syngeneic cells could be used to circumvent the problem with cell rejection. Certainly, this is a possibility as Gage teaches that syngeneic cells need not integrate into a homotypic region (Gage, 1998, Nature, 392 supplement, pages 18-24; page 18, 2nd col., 1st parag. under "Function of cells as

implants"). However, if long-term survival is required, success of the graft appears to depend on the cell type, the site of implantation, and type or class of promoter (Gage, page 19, 1st col., lines 2-5). Alternatively, if in the cases that require a cell to integrate into a homotypic region and perform specific physiological roles, a skilled artisan would need to know the phenotype of the cell and the spatial location critical to its utility (e.g. a retinal cell transplant or a skin graft) (Gage, page 19, 1st col., 2nd parag. to 2nd col., 2nd parag.). With regards to the instant invention, the specification does not teach what cells to use and where it should be transplanted in the host. In addition to selecting a cell, a skilled artisan would need to remind oneself that the transplanted cell would be comprised of a DNA expression vector. The art teaches that sometimes following transplantation, a cell comprised of a transgene may alter its level of transgene expression. For example, Fisher teaches that a neuronal cell line, RN33B, show loss of β-gal labeling in cells grafted in the CNS. The change in gene expression does not appear to be because the skilled artisan used a retrovirus. Gene expression is also compromised in cells wherein adenovirus or herpes virus vectors were used (Fisher, 1997, Neurobiology of Disease, 4: 1-22; page 15, 2nd col., 2nd parag. under "In vivo considerations of genetically modified cells," lines 1-13). Thus, for reasons described above, a xenogenic or allogeneic transplant of faces the problem of host rejection. The methods involved to reduce the chance of rejection would need to be empirically determined. Coupled with this, to reduce rejection may involve methods of reducing infection in the host. This, too, would need to be empirically determined. In the case of

syngeneic cells, a skilled artisan would need to be taught what kind of cells would need to be isolated, how to isolate said cells, and how to culture said cells. This would need to be empirically determined. Finally, whether a transgene construct can be reliably expressed would also need to be considered. Thus, for the reasons described above with regard to cell transplantation, the specification as filed does not provide sufficient guidance, working examples and evidence as to how an artisan of skill would have made and used the claimed invention commensurate with the scope of the claims without undue experimentation.

The claimed invention broadly encompasses the use of knockout non-human mammals. At the time of filing, the art teaches that the only species of non-human mammal in which knockouts can be performed is mice. This is because the art teaches that the only transgenic non-human mammalian animals that can be generated by using ES cells are mice. Further, mice are the only mammals in which ES cells can be generated and which chimerism from ES cells extend to the germline. According to Murray, et al. (1999, *Transgenic Animals in Agriculture*, CAB International: Oxon, pages 58-61), the "isolation of ES cells has not been accomplished unequivocally in other species, including in domestic livestock (Murray, et al., page 59, lines 3-4)." It is possible that putative ES cells have been isolated in other animals aside from the mouse. These include sheep, hamster, pig, cattle, mink, rabbit, rat, monkey and goat. However, in many cases the data characterizing them do not provide the most convincing data (Murray, et al., page 59, lines 10-17). Part of the discrepancy stemmed

from the fact that scientists were relying on morphological comparisons of mouse ES cells to define what other animals' ES cells should look like. Some scientists added a second level of stringency, identifying ES cells by the fact that they differentiate *in vitro*. However, the best level of stringency that identifies an ES cells is that the cells can differentiate *in vivo* (Murray, et al., page 60, second paragraph). In the case where chimeric offspring have been obtained after injection of putative ES cells into blastocysts, the species include mouse, pig, and rabbit (Murray, et al., page 59, lines 18-22). With regards to chimerism from ES cells extending to the germline, the only species in which this has been demonstrated is the mouse (Murray, et al., page 60, second paragraph, lines 19-22). Thus, the art teaches that making transgenic animals via ES cells is limited to mice. The specification does not teach how to obtain other non-human mammalian ES cells, nor does the specification teach that the ES cells obtained from other non-human mammalian extend to the germline such that knockout progeny can be generated. For this reason, a skilled artisan is not enabled for other transgenic non-human mammals made from ES cells.

While the art teaches that the technique used to generate knockout mice is well known, the art does not teach an artisan how to predict that any knockout mouse will exhibit a predictable phenotype. For example, Moreadith and Radford teach that gene targeting of the endothelin loci subsequently led to the creation of mice with Hirschsprung's disease (aganglionic megacolon) instead of the anticipated phenotype (abnormal control of blood pressure)(Moreadith and Radford, 1997, J. Mol. Med., 75: 208-216). The art teaches that despite

characterization of genes and the proteins they encode, one cannot necessarily predict what effects gene disruption will have on the mouse. It thus follows that an artisan cannot predict what effects gene disruption will have on any non-human mammal. As the specification does not teach an artisan how to reliably predict phenotypes in any gene disrupted non-human mammals, and the specification does not teach any non-human mammals comprising any gene disruptions, the specification does not enable an artisan to practice the claimed invention for the full breadth of any knockout non-human mammal.

The claimed invention broadly encompasses a genetically engineered non-human mammal wherein the mammal exhibits no phenotype. Again, returning to Hammer, et al., Hammer et al. created both transgenic mice and rats expressing the human HLA-b27 gene and beta-2 microglobulin. Although both transgenic animals bearing the HLA-b27 gene expressed the gene, transgenic mice did not show any HLA-b27 associated disease, whereas the transgenic rats demonstrated most of the HLA-b27 related diseases (Hammer, et al., page 1099, col. 2, lines 20-28). Hammer et al.'s teaching implies that the transgenic rats can be used as a model to study human disease, while the transgenic mice cannot, as the mice exhibit no phenotype. As such, the claims encompass genetically engineered non-human mammals that exhibit no phenotype. Nothing in the specification teaches how to use genetically engineered non-human mammals that exhibit no phenotype. It would be undue experimentation for an artisan to

use any genetically engineered non-human mammals that exhibit no phenotype as the specification provides no guidance.

Therefore, for the reasons described above, the specification does not provide guidance to an artisan to practice the claimed invention commensurate in scope with these claims.

Examiner's note: It should be pointed out at this time that it may seem contradictory that the Examiner has considered the breadth of any knockout mouse to be enabled and yet provides a teaching of Moreadith and Radford. However, the Examiner has considered the breadth of any knockout mouse to be enabled, with the proviso that the artisan would understand that the transgenic mice that would be used in the instant invention are the ones wherein the relationship between phenotype and gene are understood. Conversely, it is implied that an artisan would not use a knockout mouse wherein the relationship between gene and phenotype is unknown and wherein the knockout mouse has no phenotype. Similarly, with regards to transgenic mice comprising an overexpression construct, the Examiner considered the breadth of any transgenic mouse comprising an overexpression construct to be enabled with the proviso that the artisan understands the relationship between gene and phenotype.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Jonker et al. (2001, Molecular and Cellular Biology, 21: 5471-5477).

Claim 1 is to a method of predicting adverse responses to drugs effecting a target by assessing the responses of non-human mammalian models, wherein the non-human mammal is genetically engineered. Claim 2 narrows claim 1 by limiting the scope of the non-human mammal to rodent. Claim 3 narrows claim 1 by limiting the scope of the evaluation to comparing the metabonomic profile of the genetically engineered non-human mammal with a substantially identical non-engineered non-human mammal subjected to the same pre-selected perturbance. Claim 4 narrows claim 1 by limiting the scope of the metabonomic profile using urine.

Jonker et al. teach how to make a mouse comprising a disruption in the Oct1 gene. The Oct 1 gene was disrupted by replacing exon 7 with an inverted pgk-hygro cassette via homologous recombination (Jonker, et al., page 6573, 1st col., 1st parag. lines 2-4). While Jonker et al. teach that the Oct1-/- mice, on a gross level appear normal, they teach that the Oct1-/- mice, when treated with tetraethylammonium (TEA), excrete more TEA in their urine than wild type mice. the main route for TEA excretion was via the kidney. The amount of [14C]TEA

found in urine was 1.5-fold higher Oct1-/- mice and was 70.3%+/- 12.4% of the administered dose, compared to 45.7%+/- 3.4% in wild-type mice (Jonker et al., page 5473, 2nd col., 2nd parag., lines 1-4).

Jonker et al. anticipate claims 1-4 because they teach a knockout Oct1 mouse, wherein the metabonimic profile of urine, when introduced to the pre-selected perturbance of TEA, is different from that of a wild type mouse.

Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Doublier et al., (2000, Kidney International, 57 : 2299-2307).

Claim 1 is to a method of predicting adverse responses to drugs effecting a target by assessing the responses of non-human mammalian models, wherein the non-human mammal is genetically engineered. Claim 2 narrows claim 1 by limiting the scope of the non-human mammal to rodent. Claim 3 narrows claim 1 by limiting the scope of the evaluation to comparing the metabonomic profile of the genetically engineered non-human mammal with a substantially identical non-engineered non-human mammal subjected to the same pre-selected perturbance. Claim 4 narrows claim 1 by limiting the scope of the metabonomic profile using urine.

Doublier et al. teach transgenic mice comprising a nucleic acid sequence encoding the human IGFBP-1 operably linked to a human α_1-anti-trypsin promoter. Doubleier et al. teach that while there were no significant differences in the mean urinary protein/creatinine ratios between homozygous transgenic mice, heterozygous transgenic mice, and nontransgenic littermates at 3 months

of age, at 8 months of age, the homozygous transgenic mice had significantly higher urinary protein/creatinine ratios as compared with the heterozygous transgenic mice and nontransgenic littermates (Doublier et al., page 2302, 2nd col., under "Urine protein/creatinine ratios").

Doublier et al. anticipate claims 1-4 because they teach a transgenic mouse comprising human IGFBP-1, wherein the metabonimic profile of urine, is different from that of wild type mice. Here, the pre-selected perturbance is age of the mouse.

Claims 1-3, 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Moriya et al. (2000, J. of Neurosci, Res., 61: 663-673).

Claim 1 is to a method of predicting adverse responses to drugs effecting a target by assessing the responses of non-human mammalian models, wherein the non-human mammal is genetically engineered. Claim 2 narrows claim 1 by limiting the scope of the non-human mammal to rodent. Claim 3 narrows claim 1 by limiting the scope of the evaluation to comparing the metabonomic profile of the genetically engineered non-human mammal with a substantially identical non-engineered non-human mammal subjected to the same pre-selected perturbance. Claim 10 narrows claim 1 by limiting the scope of the pre-selected perturbance to reversal of the light dark cycle.

Moriya et al. teach that NR2A-/- and NR2C-/- mice were generated previously (Moriya et al., page 664, 1st col., under "Animals"; Kadotani et al., 1996 and 1998). Moriya et al. teach that wild type, NR2A-/- ,and NR2C-/- were

examined for reentrainment of locomotor activity rhythm to a 6-hr advanced light dark (LD) cycle. While no differences in reentrainment were observed between wild-type and NR2A-/- and NR2C-/- mice using high intensities of light such as 20 and 180 lux, some NR2A-/- mice exposed to low intensity light took longer than wild type and NR2C-/- to reentrain to the new LD cycle (Moriya et al., page 666, 1st col. 2nd parag. to 2nd col., 1st parag.).

Moriya et al. anticipate claims 1-3, 10 because they teach a transgenic mouse comprising disruption in NR2A, wherein, the pre-selected preturbance, changes in the light-dark cycle, results in different phenotypes from that of the wild type mouse.

In the event that the claimed pre-select perturbance of "reversal of the light-dark cycle" is not identical to those disclosed by Moriya et al., it is considered that any differences would be the result of minor variations, wherein such variants would have been obvious over the prior art. Thus, the claimed invention as a whole was at least prima facie obvious over, if not anticipated by the prior art.

Claims 1-3, 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Shen et al., (2000, PNAS, USA, 97: 11575-11580).

Claim 1 is to a method of predicting adverse responses to drugs effecting a target by assessing the responses of non-human mammalian models, wherein the non-human mammal is genetically engineered. Claim 2 narrows claim 1 by limiting the scope of the non-human mammal to rodent. Claim 3 narrows claim 1

by limiting the scope of the evaluation to comparing the metabonomic profile of the genetically engineered non-human mammal with a substantially identical non-engineered non-human mammal subjected to the same pre-selected perturbance. Claim 10 narrows claim 1 by limiting the scope of the pre-selected perturbance to reversal of the light dark cycle.

Shen et al. teach transgenic mice comprising a nucleic acid sequence encoding the human $VPAC_2$ receptor. Shen et al. teach that YAC clone HSC7E526 underwent several base changes, resulting in the placZ$VPAC_2$R clone. Shen et al. teach that transgenic mice comprising the clone were generated (Shen et al., page 11576, 1st col., parag. under "Modification of YAC Clone HSC7E526 and Production of Transgenic Mice"). Shen et al. teach that transgenic and wild type mice were entrained to the initial light dark (LD) cycle. Upon shifting the LD cycle 8 hours, the transgenic mice required less time (on average 1.5 days) to re-entrain to an 8 hour advance in the LD cycle than wild type controls. Transgenic animals also appeared to re-entrain more quickly to a phase delay of 8 hours (2.7 vs. 3.4 days) (Shen et al., page 11577-11579, see under "Behavioral Analysis").

Shen et al. anticipate claims 1-3, 10 because they teach a transgenic mouse comprising a YAC clone comprising the human $VPAC_2$ receptor, wherein, the pre-selected preturbance, changes in the light-dark cycle, results in different phenotypes from that of the wild type mouse.

In the event that the claimed pre-select perturbance of "reversal of the light-dark cycle" is not identical to those disclosed by Shen et al., it is considered

that any differences would be the result of minor variations, wherein such variants would have been obvious over the prior art. Thus, the claimed invention as a whole was at least prima facie obvious over, if not anticipated by the prior art.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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